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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LY, CHEYNE D	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,576	HUYN, NAM Q.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *11,12,19,23-38 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 13-18, 20-22, 39, 40, and 42-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-49* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/16/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments filed January 20, 2004 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. The addition of new claims 43-49 is acknowledged.

3. Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 are examined on the merits.

4. NON-FINAL OFFICE ACTION.

IDS

5. Documents J, K, and L listed in FORM PTO-1449, filed September 16, 2003, have not been considered because the instant application does not contain English-language translations to the foreign documents as is required for consideration for a reference. For a document published in a non-English-language, a copy of the translation of the document to the English-language is required. (See MPEP § 609)

CLAIM REJECTIONS - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory algorithm type subject matter.

8. Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 are rejected because said claims are directed to a method and program storage device comprising steps for determining of n>p,

k<p, reducing set of n measurements, and select values resulted from the above data manipulation step without any physical alteration step, which is considered to be non-statutory subject matter. "For example, a computer process that simply calculates a mathematical algorithm that models noise is nonstatutory. However, a claimed process for digitally filtering noise employing the mathematical algorithm is statutory." (MPEP § 2106 (IV)(B)(2) (b), part ii). Similar to the nonstatutory example above, the instant invention comprises algorithmic steps for identifying biological markers without any physical alteration resulted from the analysis.

9. It is acknowledged that claims 40 and 42 are directed to a program storage device comprising steps for analysis requiring the reducing and selecting steps. However, the steps of reducing and selecting do not cause any physical alteration outside of the program storage device resulted from the analysis.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

RESPONSE TO ARGUMENT

12. Applicant's argument by pointed to support (page 14, lines 17-24) has been fully considered and found to be unpersuasive because the pointed to citation in the specification further supports the vague and indefinite issue of the limitation of "desired computation

time". The pointed to support discloses "thresholds can be derived based on a desired computation time" and "the amount of time necessary to perform the subsequent step." In one reasonable interpretation of the pointed support, the "desired computation time", wherein said computation time can not be determined, is different "the amount of time necessary to perform the subsequent step" because the latter is empirically determined by the data set sizes.

13. Claims 21 and 22, line 1, the phrase "desired computation time" causes the claims to be vague and indefinite because it is unclear what criteria is being used to determine that the computation time is desirable. Is the computation time desirable because a specific task has been process within a time limit or simply computation time desirable is consistent with the processor speed (CPU)? Clarification of the metes and bounds is required.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 47-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

16. The limitations of "1000 or more", "5000 or more", or "10,000 or more" have not been found in the pointed to support (page 5, lines 5-7) of the instant specification as originally filed. It is acknowledged that the pointed to support discloses set of 5000 and 1000

biomarkers and 100 subjects which are completely different from "1000 or more", "5000 or more", or "10,000 or more" *n* biological measurements.

LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

19. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic

engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

20. The instant specification discloses an invention relates generally analysis of biological data for predicting clinical endpoints such as disease conditions, response to drug therapy, or disease progression (page 1, [0002]). The claimed invention is directed to a method and program storage device for identifying biological markers associated with a clinical endpoint. However, said specification does not disclose any specific clinical endpoints which have been identified with the claimed method as directed to any specific set of biomarkers.

21. It is noted that each disease condition has its own specific pathology and mechanism of action. In regard to drug therapy, each drug is specific to the disease being treated and the mechanism of action of said drug. What specific clinical endpoints are being identified with the claimed invention? Without any specificity as to the type of clinical endpoints or drugs, one of skill in the would not know how to predictably practice the claimed invention without undue experimentation.

22. Further, Applicant discloses biomarker measurements comprise soluble factor..., or amount of exercise (page 2, line 29 to page 3, line 4). Further, the type of biomarkers of the present invention include those at much lower granularity blood cell population such as CD4 T cells (page 9, [007). It is noted that the above cited biomarkers are type of measurements taken for an overwhelming number of diseases. However, these type of measurements alone are not specific to any clinical endpoints, diseases. For example, a keyword search on the NCBI PubMed site with the criteria of "CD4 and disease" generates 867 hits. The first 20 hits (search results provided as a reference) cover such diseases as AIDS, smallpox, diabetes,

cancer, arthritis, SIV, and Experimental Autoimmune Encephalomyelitis. Without any specific disclosure as to the type of markers being used for predicting clinical endpoints, how does one of skill in the art use the claimed invention with any degree of predictability?

23. Therefore, one of skill in the would not know how to predictably practice the claimed invention without undue experimentation due to the lack of disclosure of the specific type of biomarkers being used by the claimed invention to predict a clinical endpoint.

CLAIM REJECTIONS - 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in:
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

25. Claims 1-7, 13, 16-18, 20-22, 39, 40, and 42-49 are rejected under 35 U.S.C. 102(a) and (e)(2) as being clearly anticipated by Campbell et al. (US 6,059,724 A).

RESPONSE TO ARGUMENT

26. Applicant's argument has been fully considered and responded to below.

27. Specific to Applicant's argument "not all biomarkers were assessed, even when a subject made a visit and Campbell et al. does not disclose how many biomarkers were measured at

each visit, Campbell et al. discloses that in extreme example, only 88 values of Direct Bilirubin were available from only 80 subjects. However, in case of blood pressures, all available demographic data were used as potential discriminators wherein the potential biomarkers are listed in Table 2 (column 33, lines 16-20) totaling 36. Therefore, for 641 "annual" evaluations from 481 subjects, or about 1.3 annual evaluations per subject, and 36 biomarkers from Table 2 (column 33, lines 11-20), the number of biological measurements is at least (36 biomarkers X 641 evaluations) 23076 biological measurements.

28. Campbell et al. discloses a computer based system comprising a processor and database (Abstract etc. and column 9, lines 2-30), and method for predicting the future health of an individual by obtaining longitudinal data for a large number of biomarkers from a large human test population, statistically selecting predictive biomarkers, and determining and assessing an appropriate multivariate evaluation function based upon the selected biomarkers (column 1, lines 8-12).

29. For 641 "annual" evaluations from 481 subjects, or about 1.3 annual evaluations per subject, and 36 biomarkers from Table 2 (column 33, lines 11-20), the number of biological measurements is at least (36 biomarkers X 641 evaluations) 23076 biological measurements, *n*. Therefore, 23076 biological measurements for a population of 481 subjects is greater that of 641 evaluations, *p*, as in instant claim 1, line 2, claim 40, lines 4-5, and claim 46.

30. The 23076 (*n*) biological measurements for a population is reduce to a set of *m* candidate measurements (Table 2), as in instant claims 1, 39, 40, 42, step a).

31. The select biological markers from set of *m* candidate measurements wherein values of each biological marker predict a clinical endpoint such as sickle cell (Column 38, Tables 2-7), as in instant claims 1, 39, 40, 42, step b).

32. Each biomarker listed on Table 2 represents a specific type of measurement such as age of patient, albumin, etc., *k*, as in instant claim 1, lines 3-4, and claim 40, line 6.

33. Therefore, each measurement of each distinct biomarker *k* (per 1.3 annual evaluations per subject) is less than the *p*, 641 evaluations, as in instant claim 1, line 4, and claim 40, line 6.

34. The method and system of Campbell et al. is directed a general tool for predicting risks, for a selected individual, of a wide range of diseases (condition) and monitoring the preventive measures taken (response to therapy) so as to reduce future health risks for that specific individual (column 4, lines 39-49). The method comprises 1.3 (time) annual evaluations per subject (column 33, lines 10-11). Table 1 (column 11) illustrates a list of clinical classes as directed to a patient's health, as in instant claims 2 and 43-45.

35. As cited above, *n* is 23076 biological measurements in a test population of 481 and *p* 641 evaluations; therefore, 10 *p* (6410) is less than *n,* 23076 biological measurements, as in instant claims 4, 39, line 2, and 42, line 5.

36. Further, *k* (per 1.3 annual evaluations per subject) (column 33, lines 11-20) is less 128, which is the value of *p* equal to 641 divided by 5, as in instant claim 5.

37. The method of Campbell et al. is directed to on-going assessment and monitoring the health risks of an individual (continuous response variable) (column 4, lines 44-49), as in instant claim 3.

38. The method of Campbell et al. comprises a step for correlation analysis for determining individual's membership in one of two complementary groups of subjects and the explanatory variables are typically biomarkers or functions of biomarkers (column 7, lines 55-67 to column 8, lines 1-9), as in instant claim 6.

39. The biomarkers values are clustered (column 10, lines 44-53), as in instant claim 7.

40. The 23076 biological measurements, *n*, are derived from 481 subjects (different sources) (column 33, lines 11-20), as in instant claims 13 and 47-49.

41. The biomarkers include all that can be measured in biological samples (column 10, lines 53-56). Further, the said method measures the biomarker values of selected large sets of biomarkers simultaneously (parallel) (column 15, lines 66-67 to column 17, lines 1-2) as in instant claims 16-18.

42. The computer system of Campbell et al. comprises a means for selecting from said biomarkers, *k*, a subset of biomarkers for discriminating between members belonging to the subpopulations D and D, wherein the subset of biomarkers is selected based on distributions of the biomarker values of the individual members of the test population (Abstract etc.), as instant claim 20.

43. Campbell et al. discloses estimating quantitatively, for each member of the test population, the probability of acquiring the specified biological condition within the specified time period or age interval (Abstract etc.) as in instant claims 21 and 22.

CLAIM REJECTIONS - 35 USC § 103

44. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

45. (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

46. Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell et al. (US 6,059,724 A) taken with Perou et al. (August 2000) in view of Lucas et al. (US 5,871,946 A).

RESPONSE TO ARGUMENTS

47. Applicant's argument of the purposes and approaches disclosed by Eisen et al. are different from that of Campbell et al. because the approach of Eisen et al. is not to locate specific features capable of classifying patients, but rather to cluster different genes into functional classes has been fully considered and responded to below.

48. Specific to Applicant's argument directed to the disclosure of Lucas et al., said argument has been fully considered and found to be unpersuasive as discussed below. It is re-iterated that Lucas et al. discloses a method of studying biological surface markers (column 42, lines

16-18) and ranking cells by the functional activity of the cell markers (column 33, lines 44-46). The disclosure of ranking cells by the functional activity of the cell markers is consistent with limitation of biological markers of instant claims 14 and 15.

49. Further, Applicant argues that Lucas et al. does not relate to methods of efficiently mining broad data sets and the method of Lucas et al. is necessarily of limited scope and requires domain knowledge. The limitations of methods for efficiently mining broad data sets; and not necessarily of limited scope and does not require domain knowledge have not been found in the instant set of claims reciting the elected subject matter. It is noted that claims are given their broadest interpretation consistent with the specification. However, the instant claims are not limited to the critical steps that have been cited from the specification by Applicant as limitations that are not disclosed by Lucas et al. As cited by the MPEP, the court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.). See also In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) (MPEP §2111 [R-1]).

50. Campbell et al. discloses the limitations of claims 1-7, 13, 16-18, 20-22, 39, 40, and 42-49 as discussed above.

51. Further, Campbell et al. discloses a method that requires relatively precise calculations of statistical significance (column 23, lines 8-13) and the threshold is set to be between 0 and 1 standard deviation (column 23, lines 60-63).

52. However, Campbell et al. does not disclose the limitations of correlation based on hierarchical cluster, user-selected correlation threshold and ranking of biological markers as recited in claims 8-10, 14, and 15.

53. Perou et al. discloses a method for performing hierarchical clustering analysis to organize the experimental samples only on the basis of overall similarity in the gene expression patterns (biological markers) (page 749, column 2, lines 6-10). The method of Perou et al. is used to characterize specimens of human breast tumors from 42 different individuals (page 747, column 2, lines 7-11), as in instant claim 8.

54. It is noted that the system of Campbell et al. is directed to a general tool for quantitatively predicting risk, for a selected individual, of a wide range diseases (column 4, lines 39-43), thus, suggesting the said system and method are directly applicable to analyzing any biological marker gene expression.

55. Lucas et al. discloses a method of studying biological surface markers (column 42, lines 16-18) and ranking cells by the functional activity of the cell markers (column 33, lines 44-46), as in instant claims 14 and 15.

56. The method of Lucas et al. further comprises a user using a system for inputting numeric values to control the output thresholds (column 49, lines 7-11 and 24-28), as in instant claims 9 and 10.

57. Campbell et al. discloses the need for improvements in the methods of diagnosis and treatment of disease to discovering preventive measures by analyzing data directed to biomarkers (column 1, lines 20-26 and column 5, lines 50-55). The general system and method of Campbell et al. is directly applicable to biological marker data of Perou et al. and Lucas et al.

58. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated the improvements emphasized by Campbell et al. and improve on the concept by bringing a holistic approach to develop an integrated understanding of a biological system by using hierarchical clustering analysis to organize the experimental samples only on the basis of overall similarity in the gene expression patterns (biological markers) (page 749, column 2, lines 6-10) as taught by Perou et al. An artisan of ordinary skill in the art would be further motivated to reliably predict future health problems as directed to the biomarkers identified by the method of Lucas et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use a computer system and method for using hierarchical clustering to analyze large data sets such as biological markers to reliably predict future health problems as taught by Campbell et al. taken with Perou et al. wherein the said system accepts user inputs as taught Lucas et al.

CONCLUSION

59. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61

(November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 872-9306.

60. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

61. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

62. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

C. Dune Ly
4/14/04

Ardin H. Marschel
ARDIN H. MARSCHEL
PRIMARY EXAMINER
4/17/04